# LETTERS TO THE EDITOR

## No evidence for the involvement of interleukin 2 or the immunoglobulin heavy chain gene cluster in determining genetic susceptibility to multiple sclerosis

Here we report the investigation of two promising candidate multiple sclerosis susceptibility genes. Each is biologically plausible, having a function suggesting possible involvement in the pathogenesis of the disease and positional, having existing linkage evidence supporting its candidature. The two differ, however, in the origin of the supporting linkage evidence. This comes mainly from the analysis of animal models in the case of interleukin 2 (IL-2)[1] and from human studies in the case of the immunoglobulin heavy chain gene cluster.[2]

Interleukin 2 is a cytokine intimately involved with both the function and regulation of the immune system. It has both proinflammatory and anti-inflammatory actions, promoting T cell proliferation during cell mediated immune responses and, conversely, being crucial both for the development and maintenance of self tolerance. Genetic analysis of experimental autoimmune encephalomyelitis (EAE) provides strong evidence supporting the candidacy of IL-2 as a susceptibility gene.[1]

The immunoglobulin heavy chain gene cluster is another highly promising candidate. Plasma cells and B lymphocytes are readily detected in areas of acute demyelination and the occurrence of oligoclonal immunoglobulin bands in the spinal fluid of affected people is a distinctive feature of the disease. Moreover, the cluster is encoded towards the telomere of chromosome 14q where linkage evidence from the United Kingdom sibling pair families is at its strongest (lod score≈3.0).[2]

The gene for IL-2 is encoded on chromosome 4q26. To investigate its role as a susceptibility factor in multiple sclerosis, we typed a closely encoded microsatellite marker in 502 trio families (both parents and a single affected offspring). Transmission disequilibrium testing (TDT)[3] of these data disclosed no significant evidence for linkage disequilibrium (table). The expression of IL-2 is under the control of transcription factor 8 (TCF8),

the gene for which is encoded on chromosome 10p11.[4] Because variation in IL-2 expression could contribute to susceptibility of multiple sclerosis, we also typed a microsatellite encoded close to the TCF8 gene in the same 502 families. Again, the TDT results (table) were negative.

We typed three microsatellite markers encoded within the immunoglobulin heavy chain gene cluster in 460 simplex families. Once again TDT failed to show evidence for linkage disequilibrium (table) at any of these markers. As the markers are encoded within a 200 kb region, we also subjected them to multipoint TDT analysis but no haplotypes showing significant transmission distortion were found.

These results suggest that neither of the tested candidates has any major effect in determining genetic susceptibility to multiple sclerosis. However, in considering these data it is important to remember that the negative results could represent a type II error as, even with the large numbers of simplex families used, the power of this type of candidate gene study is limited when the effects attributable to the susceptibility genes are modest. A further possibility is that the available evidence for linkage is falsely positive and that, in fact, no susceptibility genes are encoded in these regions. The lod score observed in the immunoglobulin heavy chain gene cluster region is significantly short of the 5% genomewide significance threshold suggested by Lander and Kruglyak (lod score=4.0).[5] A third possibility is that the linkages are genuine but unrelated to the candidates we have tested. We favour this explanation with the available data suggesting that alternative candidates from these regions are responsible for the observed linkages.

ROBERT FEAKES
STEPHEN SAWCER
BELINDA SMILLIE
JEREMY CHATAWAY
SIMON BROADLEY
ALASTAIR COMPSTON
*University of Cambridge Neurology unit,
Addenbrooke's Hospital, Hills Road, Cambridge,
CB2 2QQ, UK*

DAVID CLAYTON
*MRC Biostatistics Unit, Institute of Public Health,
University Forvie Site, Robinson Way, Cambridge,
CB2 2SR, UK*

ALASTAIR COMPSTON

*ED Adrian Building, University Forvie Site, Robinson
Way, Cambridge, CB2 2SR, UK*

Correspondence to: Professor Alastair Compston
alastair.compston@medschl.cam.ac.uk

1 Encinas JA, Wicker LS, Peterson LB, *et al*. QTL influencing autoimmune diabetes and encephalomyelitis map to a 0.15-cM region containing IL2. *Nat Genet* 1999;**21**:158–160.
2 Feakes R, Chataway J, Sawcer S, *et al*. Susceptibility to multiple sclerosis and the immunoglobulin heavy chain gene cluster. *Ann Neurol* 1998;**44**:984.
3 Spielman RS, Ewens WJ. The TDT and other family-based tests for linkage disequilibrium and association. *Am J Hum Genet* 1996;**59**: 983–9.
4 Williams TM, Moolten D, Burlein J, *et al*. Identification of a zinc finger protein that inhibits IL-2 gene expression. *Science* 1991;**254**:1791–4.
5 Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* 1995;**11**: 241–7.
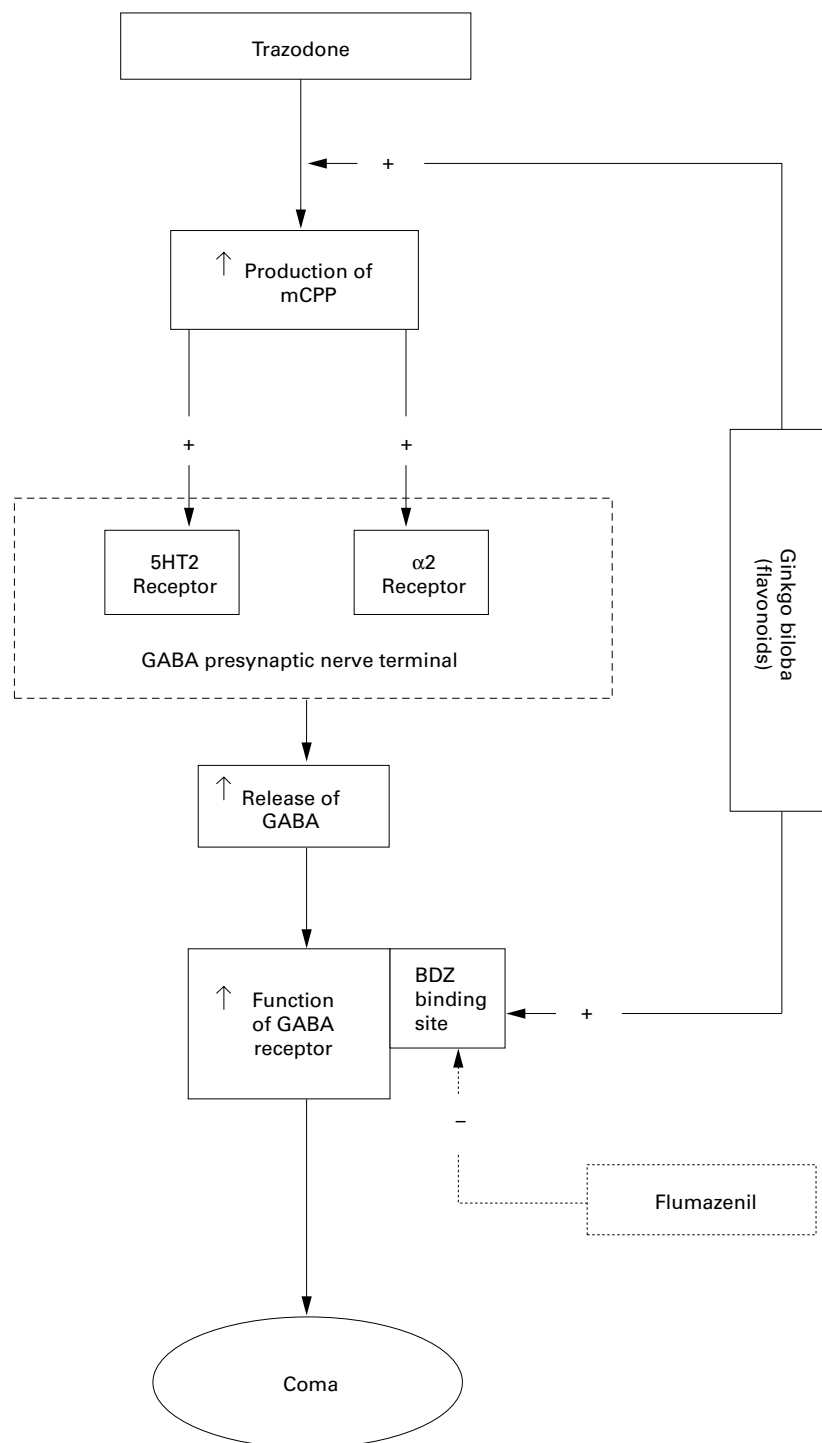
## Coma in a patient with Alzheimer's disease taking low dose trazodone and ginkgo biloba

We describe a patient with Alzheimer's disease who developed coma a few days after starting low dose trazodone associated with ginkgo biloba. Coma was reversed by flumazenil, a specific antagonist of the benzodiazepine (BDZ) receptor. The finding is relevant in that, although the sedative effects of trazodone are well known, the drug is inactive on the BDZ receptor. On the other hand, ginkgo is active on the receptor, but sedation has so far never been reported.

In March 1999, an 80 year old woman was first evaluated in our facility and given a diagnosis of probable Alzheimer's disease (NINCDS-ADRDA criteria) of a moderate severity (mini mental state examination of 10/30). She had no physical comorbidity or vascular risk factors. At the time of observation she was taking 3.5 mg bromazepam for mild restlessness, anxiety, and irritability, with only partial benefit (neuropsychiatric inventory: anxiety 4/12, irritability/lability 3/12). A dose of 5 mg donepezil at bedtime was added with the aim of improving both cognitive function and behaviour, together with 600 mg vitamin E twice daily.

After 3 months, no improvement of cognitive function, behaviour, or daily function could be detected. Donepezil was discontinued. Vitamin E was also discontinued due to the development of ecchimotic bruises on all limbs. Ginkgo biloba ((Egb 761) 80 mg) twice daily was added. Rivastigmine was not considered a feasible option because it was not possible to have frequent clinical follow up visits during the titration phase. For a better control of behavioural disturbances, bromazepam was replaced with 20 mg trazodone twice daily.

The day after the visit, the new therapeutical regimen was initiated. Sedation or other adverse effects did not appear, and the care giver reported improvement of anxiety. On the next day, the improvement of behavioural disturbances was sustained, still in the absence of sedation. At 600 pm of the third day, the patient developed instability of gait and drowsiness. At 700 pm she fell asleep. The care giver tried to wake her by slapping her face, but without success. Overall, she had taken 100 mg trazodone and 320 mg Egb 761 in about 50 hours. A physician on call found that blood pressure was 120/55 mm Hg and her Glasgow coma scale was 6/15. The patient was taken to the nearest hospital,

*Table 1  Transmission disequilibrium testing results*

| Marker | Het | $\chi^2$ | df | p Value | Primers |
|---|---|---|---|---|---|
| IL2 | 0.89 | 7.31 | 4 | 0.12 | AAA GAG ACC TGC TAA CAC |
|  |  |  |  |  | TGT TTC CCC TTG CCG CC |
| TCF8 | 0.73 | 0.08 | 2 | 0.96 | AGA GGA TCC TGT TCA CTA CTG |
|  |  |  |  |  | TGC GAA TTC TTA CTA GGT CTG AGG |
| D14S1419 | 0.56 | 2.31 | 3 | 0.51 | TAG GGA CAG GCA GTT GAT TA |
|  |  |  |  |  | CAA TTA ATG TAA AAA TTA GCC A |
| D14S1420 | 0.67 | 0.74 | 2 | 0.69 | TGT TTG AAG AAG GGA GTC GT |
|  |  |  |  |  | CCC ACT CCA TGT CTT CTG TT |
| D14S826 | 0.74 | 1.74 | 4 | 0.78 | TCT CTA AAG CTA CTA TAA CCC AG |
|  |  |  |  |  | TGC TGT TGG ACT CAG GTA GCT A |

Each microsatellite was amplified by PCR from genomic DNA with fluorescent labelling of the forward primer and genotyped using the Applied Biosystems GENESCAN/GENOTYPER system (primers as shown in table). TDT was performed using the TRANSMIT program version 2.5, considering only those alleles with a frequency of greater than 10% (corresponding to the number of degrees of freedom {df} in the table). The chromosome 14 markers are listed in map order.
The families were recruited from throughout the United Kingdom. All are white and the affected offspring meet the Poser criteria, 95% having clinically definite, category A or B, disease.

*Pathway from trazodone to coma.*

mented. Drowsiness is a dose dependent effect due to a direct antagonism at the α1 adrenergic receptor level, and in elderly people it has been reported with doses greater than 75 mg daily. Trazodone is metabolised by an isoform of cytochrome *P*-450 (CYP3A4) into an active compound 1-(m-chlorophenyl)piperazine (mCPP). Through an agonistic action on presynaptic 5-HT2 and α2 receptors located on GABAergic nerve terminals,[2] mCPP enhances the release of GABA.[3 4] The activity of CYP3A4 can be increased by flavonoids.[5]

We hypothesise that, in our patient, on the one hand flavonoids provided a subclinical increase of the GABAergic activity through a direct effect on the BDZ receptor, whereas on the other increased CYP3A4 function and mCPP production, inducing a further enhancement of GABAergic activity that became clinically apparent. Flumazenil might have blocked the direct effect of flavonoids, thus causing GABAergic activity to fall below the threshold of clinical manifestation (figure).

Ginkgo is widely used and is thought to be a harmless food supplement. Although we warn that the adverse effects of the simultaneous administration of trazodone and ginkgo should be further confirmed, we think that natural compounds such as ginkgo can have, in some clinical circumstances, adverse effects of similar magnitude as traditional drugs.

SAMANTHA GALLUZZI
*Laboratory of Epidemiology and Neuroimaging, IRCCS San Giovanni di Dio - FBF, via Pilastroni 4, 25125 Brescia, Italy*

ORAZIO ZANETTI
GIULIANO BINETTI
*Alzheimer's Unit*

MARCO TRABUCCHI
*Department of Pharmacology, II University of Roma, Italy*

GIOVANNI B FRISONI
*Laboratory of Epidemiology and Neuroimaging, IRCCS San Giovanni di Dio - FBF, via Pilastroni 4, 25125 Brescia, Italy*

Correspondence to: Dr Giovanni B Frisoni frisoni@master.cci.unibs.it

1 Medina JH, Viola H, Wolfman C, *et al.* Overview-flavonoids: a new family of benzodiazepine receptor ligands. *Neurochem Res* 1997;**22**:419–25.
2 Hamik A, Peroutka SJ. 1-(m-Chlorophenyl)piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. *Biol Psychiatry* 1989;**25**:569–75.
3 Shen RY, Andrade R. 5-Hydroxytryptamine2 receptor facilitates GABAergic neurotransmission in rat hippocampus. *J Pharmacol Exp Ther* 1998;**285**:805–12.
4 Pittaluga A, Raiteri M. GABAergic nerve terminals in rat hippocampus possess α2-adrenoceptors regulating GABA release. *Neurosci Lett* 1987;**76**:363–7.
5 Koley AP, Buters JTM, Robinson RC, et al. Differential mechanisms of cytochrome P450 inhibition and activation by α-naphthoflavone. *J Biol Chem* 1997;**272**:3149–52.

## Bickerstaff's brainstem encephalitis subsequent to *Campylobacter jejuni* enteritis

Bickerstaff's brainstem encephalitis (BBE) is characterised by acute ophthalmoplegia and ataxia preceded by infection.[1] BBE rather than Miller Fisher syndrome is usually diagnosed for patients who show drowsiness and have brisk reflexes, extensor plantar responses, and long tract sensory disturbance. Bickerstaff and Cloake[1] speculated that the aetiology of BBE is similar to that of

where 1 mg flumazenil intravenously was administered. The patient awoke immediately.

Medicine bottles at the patient's home were examined. The medications remaining in the containers were consistent with the prescribed doses, and medications other than those prescribed were not found anywhere in the house.

Trazodone and ginkgo were discontinued and bromazepam was resumed. The patient was re-evaluated 2 months later. Cognitive functions and behaviour were unchanged.

The pathogenesis of coma would have remained unexplained in this patient had not

flumazenil been fortuitously administered. This led to an investigation of the links among trazodone, ginkgo, and the GABAergic system.

Ginkgo biloba is active on cognition in Alzheimer's disease through its antioxidant properties. Flavonoids represent the major active component of the extract and possess GABAergic activity through action at the BDZ binding site as partial agonists.[1] However, ginkgo alone does not have clinically sedative effects.

Trazodone is an antidepressant widely used for its hypnotic and sedative effects to treat behavioural disturbances in the de-

Guillain-Barré syndrome (GBS) because areflexia and CSF albuminocytological dissociation was detected in one of their three patients. Because prior infection is frequent in BBE, as in GBS, autoimmune mechanisms produced by microbial infections may function in its pathogenesis. A review of the literature in English turned up eight cases of BBE in which the pathogens of antecedent infection had been identified. The reported antecedent infections in BBE are herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, measles virus, *Salmonella typhi*, and *Mycoplasma pneumoniae*. We here describe a case of BBE subsequent to *Campylobacter jejuni* enteritis.

A 17 year old youth had fever and diarrhoea that cleared up over a period of 5 days. Eight days after the resolution of this illness, he experienced unsteady gait (day 1), and the next day he required assistance to walk and experienced vertigo. On day 3, he could no longer walk and vomited several times. He was apyrexic but drowsy. The pupils were normal and responded promptly to light. There was no limitation of ocular movement. Bifacial palsy was present, and there was mild weakness in the four limbs. Tendon jerks were brisk. Babinski's sign was negative. Paraesthesias of the glove and stocking type were present. The white blood count, C reactive protein, and erythrocyte sedimentation rate were normal. Protein in CSF was 30 mg/dl with 7 cells/μl. The tentative diagnosis was brainstem encephalitis. Acyclovir was given intravenously for 5 days and methylprednisolone for 3 days. Brain MRI showed no brain abnormality on days 5 and 12. On day 7, the patient became confused. Upward gaze and lateral gaze to the left were impossible, and downward and lateral gaze were moderately impaired. Bell's phenomenon and oculocephalic reflexes were absent. He developed palatal and lingual weakness. Muscular weakness was severe in the distal part of the arms and moderate in the legs. On day 8, motor and sensory nerve conduction velocities were normal, but an EEG showed bilateral diffuse θ and δ activity at rest. He was given 0.2 g/kg human immunoglobulin (Venilon®, Teijin, Tokyo, Japan) daily for 5 days starting on day 8. Consciousness disturbance lessened from day 9, and he became fully conscious on day 12. Facial and oropharyngeal weakness disappeared on day 13. On day 17, there was no paresis of the extraocular muscles, except for upward gaze limitation of the right eye. Limb power returned to normal on day 19. On day 22, he could walk, but his gait was markedly ataxic. An EEG was normal on day 29. Ataxic gait and gaze limitation disappeared respectively on days 30 and 39. Proprioceptive sensation was not impaired during the course of this illness. Thin layer chromatography with immunostaining showed that on day 3 his serum IgG reacted with GQ1b and GT1a, but not with GM1, GD1a, GD1b, or GT1b. The *C jejuni* which grew from stool cultures taken on day 3 belonged to Penner's serogroup D (corresponding to PEN 4, 13, 16, 43, and 50) in the modified Penner's serotyping system,[2] and to LIO 1 in Lior's serotyping scheme. An enzyme linked immunosorbent assay showed strongly positive serum anti-*C jejuni* antibody on day 3 (IgM, 4000; IgG, 64 000; IgA, 16 000). Viral screening (including herpes simplex virus) of the blood and CSF was unremarkable.

The gram negative bacterium *C jejuni*, the most often identified trigger pathogen in GBS, may also be a trigger for Miller Fisher syndrome and encephalopathy. Subsequent to *C jejuni* enteritis, our patient showed consciousness disturbance (drowsiness and confusion), hyperreflexia, and tetraparesis as well as external ophthalmoplegia and ataxia of the cerebellar type. Serology and isolation of the bacterium from his faeces confirmed prior *C jejuni* infection. BBE was diagnosed because five (cases 6, 7, 8, 13, and 18) of the 18 patients with BBE described by Al-Din *et al*[3] (Bickerstaff being one of the authors) had limb weakness. This diagnosis was supported by the presence of anti-GQ1b IgG antibody, a serological marker of BBE and Miller Fisher syndrome.[4] Overlapping BBE and GBS was another possible diagnosis, and this has been reviewed elsewhere.[5] The presence of BBE (or overlapping BBE and GBS) after infection by *C jejuni* supports the speculation that BBE and GBS are closely related and that BBE is an autoimmune disorder that occurs after microbial infection.

We previously reported the occurrence of GBS in two family members after *C jejuni* infection.[6] The clinical features of that second case are very similar to those of the case reported here; the patient was comatose and showed external ophthalmoplegia. Overlapping GBS and BBE, therefore, could also be diagnosed for that patient. Anti-ganglioside serology testing was not possible because no serum was kept. Aspinall *et al*[7] proposed that the lipopolysaccharide of the strain OH 4384 isolated from that patient with GBS has a GT1a-like structure. We partially confirmed this using anti-GT1a monoclonal antibody but in addition showed that OH 4384 has lipopolysaccharides that bear GM1, GM2, GD1a, GD2, GD3, GT1b, or GQ1b epitopes.[8] Goodyear *et al*[9] immunised mice with the lipopolysaccharide from OH 4384 and cloned three monoclonal antibodies with GQ1b reactivity. Anti-GQ1b IgG usually cross reacts with GT1a, and GQ1b is abundantly expressed in human ocular motor nerves.[10] Infection by *C jejuni* bearing a GT1a-like or GQ1b-like lipopolysaccharide may induce the production of anti-GQ1b IgG antibody, which then may bind to ocular motor nerves causing paresis of the extraocular muscles in patients with overlapping BBE and GBS.

Effective therapy for BBE has yet to be established. As stated above, BBE and GBS are closely related; therefore, steroids should not be used to treat BBE. Instead, the established treatments for GBS, plasmapheresis and intravenous immunoglobulins (IVIg), should be used. Some patients with BBE have responded favourably to plasmapheresis,[4] and the patient in our case responded favourably to IVIg. We recommend not giving steroids, but using IVIg (or plasmapheresis) to treat BBE. Controlled clinical trials are required to establish the efficacy of these procedures as therapeutic for BBE.

NOBUHIRO YUKI
MASAAKI ODAKA
KOICHI HIRATA

Department of Neurology, Dokkyo University School of Medicine,Kitakobayashi 880, Mibu, Shimotsuga Tochigi,321–0293 Japan

Correspondence to: Dr N Yuki
yuki@dokkyomed.ac.jp

1 Bickerstaff ER, Cloake PCP. Mesencephalitis and rhombencephalitis. *BMJ* 1951;ii:77–81.
2 Yuki N, Takahashi M, Tagawa Y, *et al*. Association of Campylobacter jejuni serotype with antiganglioside antibody in Guillain-Barré syndrome and Fisher's syndrome. *Ann Neurol* 1997;**42**:28–33.
3 Al-Din AN, Anderson M, Bickerstaff ER, *et al*. Brainstem encephalitis and the syndrome of Miller Fisher: a clinical study. *Brain* 1982;**105**:481–95.
4 Yuki N, Sato S, Tsuji S, *et al*. An immunologic abnormality common to Bickerstaff's brain stem encephalitis and Fisher's syndrome. *J Neurol Sci* 1993;**118**:83–7.
5 Yuki N, Wakabayashi K, Yamada M, *et al*. Overlap of Guillain-Barré syndrome and Bickerstaff's brainstem encephalitis. *J Neurol Sci* 1997;**145**:119–21.
6 Yuki N, Tsujino Y. Familial Guillain-Barré syndrome subsequent to Campylobacter jejuni enteritis. *J Pediatr* 1995;**126**:162.
7 Aspinall GO, McDonald AG, Pang H, *et al*. Lipopolysaccharides of Campylobacter jejuni serotype O:19: structures of core oligosaccharide regions from the serostrain and two bacterial isolates from patients with the Guillain-Barré syndrome. *Biochemistry* 1994;**33**:241–9.
8 Yuki N, Handa S, Tai T, *et al*. Ganglioside-like epitopes of lipopolysaccharides from Campylobacter jejuni (PEN 19) in three isolates from patients with Guillain-Barré syndrome. *J Neurol Sci* 1995;**130**:112–6.
9 Goodyear CS, O'Hanlon GM, Plomp JJ, *et al*. Monoclonal antibodies raised against Guillain-Barré syndrome-associated Campylobacter jejuni lipopolysaccharides react with neuronal gangliosides and paralyze muscle-nerve preparations. *J Clin Invest* 1999;**104**:697–708.
10 Chiba A, Kusunoki S, Obata H, *et al*. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology* 1993;**43**:1911–7.

## Myelopathy associated with Hashimoto's disease

Encephalopathy associated with Hashimoto's disease was first reported by Brain *et al* in 1966.[1] Hashimoto's encephalopathy is a steroid responsive relapsing disorder associated with Hashimoto's disease that often presents with stroke-like episodes, myoclonus, and cognitive impairment. Diagnostic testing usually shows a euthyroid state with increased thyroid autoantibodies, increased CSF protein, and EEG abnormalities.[2 3] We present the first case of myelopathy associated with Hashimoto's disease, followed 2 months later by encephalopathy.

A 70 year old housewife was admitted to our hospital on 28 July 1997. Her leg had felt heavy for a month, and she was unable to walk for several days before admission due to weakness in the left leg. She had been diagnosed with Hashimoto's disease at the age of 57 and treated with thyroxin. On January 11 1988, she had developed dysesthesia and weakness in the left arm and leg. Brain CT, radiography of the cervical spine, and CSF findings were normal at this time. She gradually recovered after this. On 31 January 1997, she was experiencing weakness in her left leg, which gradually disappeared over 2 months.

On physical examination, the blood pressure was 114/62 mm Hg. She had marked scoliosis. Neurological examination indicated a decrease of pain and temperature sensations on the right side and decrease of position and vibration sensations on the left side of the body below the Th7 level. Her muscle

strength was evaluated as 2/5 (grade) in the left lower limb and 3/5 in the right lower limb by manual muscle test. Extensor plantar response was present on the left. Routine haematological and blood chemistry findings were within the normal range except for a mild increase of glutamic oxaloacetic transaminase (46 U/l, normal range 10 to 27), glutamic pyruvic transaminase (45 U/l, normal range 5 to 33) and r-globulin (34%, normal range 9.0 to 18.3). The serum free triiodothyronine, 3.1 pg/ml (normal range 2.4 to 4.5), free thyroxine, 1.2 ng/dl (normal range 0.8 to 1.7), and thyroid stimulating hormone (TSH) concentrations, 4.84 µU/l (normal range 0.3 to 5.0), were normal. The antithyroglobulin antibody titre was 1/409600 and the antithyroid microsomal antibody titre was 1/102400. Serological tests for syphilis and HTLV-I were negative. Vitamin $B_{12}$, folate, angiotensin converting enzyme, ANA, anti-ds-DNA, ENA complex, and antiphospholipid antibody were normal or negative. Concentrations of circulating immune complexes were raised in blood (3.9 µg/ml, 0 to 2.9). The CSF was under normal pressure and contained 3 lymphocytes/µl, glucose 59 mg/dl, and mildly raised protein concentration at 50 mg/dl. Oligoclonal bands and myelin basic protein were absent. IgG index was normal. Further immunological results showed the titre of antithyroid microsomal antibodies in the CSF to be 1/128 and the titre of antithyroglobulin antibodies in the CSF to be 1/1600. A thoracic spinal MRI examination and myelography showed normal findings. She was given 500 mg intravenous methylprednisolone for 3 days. A few days later she made a marked improvement in muscle strength in her feet.

On 10 August 1997 she developed an abrupt onset of somnolence and disorientation. She was afebrile. Subsequently her respiration became irregular with short apnoeic spells. Funduscopic examination was normal. She had spontaneous myoclonus in her right arm. Repeated CSF investigations showed a predominantly mononuclear pleocytosis (9 cells/µl) and raised protein concentration (74 mg/dl). An EEG showed diffuse slowing of background rhythm with sharp waves in anterotemporal regions. Assuming a meningoencephalitis of possible viral origin, acyclovir was administered intravenously for 10 days. Polymerase chain reaction (PCR) studies for herpes simplex virus and herpes zoster virus were negative. She was given 500 mg intravenous methylprednisolone for 3 days, then oral predonisolone. Her level of consciousness improved rapidly over the next several days. She was fully alert 7 days after initiation of steroid therapy. Steroid dosage was slowly tapered and maintained at 10 mg daily. She remained well for 18 months on steroid therapy. Cerebral MRI disclosed bilateral high signal areas in frontal deep white matter on T2 weighted images. These findings were similar to those seen before her encephalopathy. Repeat spine MRI on 5 September 1997 showed previously unrecognised high intensity area by the T2 weighted image, on the left side of the cord at the level of the fifth and sixth thoracic vertebrae (figure).

Our patient had Hashimoto's disease with a marked increase in antithyroid antibodies. Her thyroid function tests were normal on thyroxin replacement therapy. Diffusely abnormal EEG and high CSF protein were found at her confusional state. Her encephalopathy markedly responded to steroid therapy. Other aetiologies
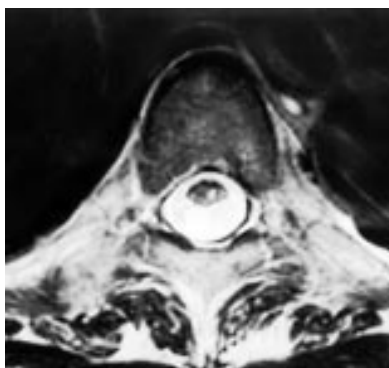


*Axial T2 weighted MRI of the thoracic spine at T5-T6 showing a high intensity area on the left side of the cord.*

such as infectious, metabolic, toxic, neoplastic, vascular, and paraneoplastic causes had been excluded. These findings are consistent with previously described cases of Hashimoto's encephalopathy.

What is notable in our case is that the myelopathy developed 2 months before encephalopathy. Some diseases, including multiple sclerosis, scoliosis, and vascular accident, are known to cause myelopathy. The lack of typical findings of brain MRI and oligoclonal bands as well as myelin basic protein in CSF, and normal IgG index were not compatible with multiple sclerosis. Findings of myelography and spinal MRI suggested that myelopathy was not associated with scoliosis. Slow progression over a month and the distribution of sensorimotor disturbance were not compatible with vascular accident. We think that her myelopathy was also associated with Hashimoto's disease because she subsequently had encephalopathy and other conditions which could cause myelopathy were excluded. This is the first case of myelopathy associated with Hashimoto's disease.

The aetiology and the pathological basis of Hashimoto's encephalopathy are not known. Brain *et al*[1] described localised cerebral oedema as a possible cause of Hashimoto's encephalopathy. This hypothesis may be supported by reversible MRI abnormalities[4] and excellent response to steroid therapy.[2 3] Ishii *et al*[5] postulated that a toxic effect of TRH on the CNS had an important role in Hashimoto's encephalopathy.

In our patient, antithyroid antibodies were detectable not only in serum but also in CSF. Shaw *et al*[2] reported that antithyroid antibodies were detectable in CSF from one of four patients with Hashimoto's encephalopathy. Marked higher titres of antithyroid antibodies in serum compared with those in CSF in our patient might suggest that antithyroid antibodies in CSF were mainly derived from serum.

TSUTOMU AZUMA
TOMOYUKI UEMICHI
MASAHIRO FUNAUCHI
SHIZURU DOI
TSUYOSHI MATSUBARA
*Second Department of Internal Medicine and Clinical Laboratory, Osaka Medical Center for Cancer and Cardiovascular Diseases, Higashinari-ku, Osaka,537–8511,Japan*

Correspondence to: Dr Tsutomu Azuma
azumat@yahoo.co.jp

1 Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. *Lancet* 1966;ii:512–14.

2 Shaw PJ, Walls TJ, Newman PK, *et al*. Hashimoto's encephalopathy: a steroid-responsive disorder associated with high anti-thyroid antibody titers- report of 5 cases. *Neurology* 1991;**41**:228–33.
3 Kothbouer- Margreiter I, Sturzenegger M, *et al*. Encephalopathy associated with Hashimoto's thyroiditis: diagnosis and treatment. *J Neurol* 1996;**243**:585–93.
4 Bohnen NILJ, Parnell KJ, Harper CM. Reversible MRI findings in a patient with Hashimoto's encephalopathy. *Neurology* 1997;**49**:246–7.
5 Ishii K, Hayashi A, Tamaoka A, *et al*. Thyrotropin-releasing hormone-induced myoclonus and tremor in a patient with Hashimoto's encephalopathy. *Am J Med Sci* 1995;**310**: 202–5.

# BOOK REVIEWS

**Mild Head Injury. A Guide to Management.** By PHILIP WRIGHTSON and DOROTHY GRONWALL. (Pp 182). Published By Oxford University Press, Oxford, 1999. ISBN 0-19-262939-5.

Mild head injury presents the neurosurgeon with several dilemmas. Those of us who see head injury cases for the purposes of medico-legal reports have even greater problems with the topic. In particular, any statistics relating to the frequency of the condition or its possible complications are likely to be unreliable as many patients who sustain mild head injuries may never be referred to neurosurgeons or even to hospital. Of those who do get admitted, in many cases the primary injury is to another body system and the coexistence of mild head injury is consequently ignored. Similarly, those patients who have continuing neurological symptoms after mild head injury may not readily come to the notice of the neurosurgeon. At best, therefore, all scientific papers and other reports which purport to give the incidence of this condition or of its complications should carry a health warning "to be treated with great caution". However, this guide to the management of mild head injury begins in an admirable way by establishing carefully both the basis on which its statistics are derived and its authors' own definition of what they mean by "mild head injury". Thus the statistics which these authors provide are likely to prove more reliable than most. Their careful studies indicate a probable incidence of 3% of persisting symptoms 28 days or more after mild head injury.

Although the view that the "post-traumatic" or "postconcussion" syndrome is a "litigation induced neurosis" still has some currency, particularly in legal circles, there are now sufficient pathological and imaging studies to agree a probable pathological basis for the syndrome. This volume sets out the evidence for such a case in a clear and lucid manner including some mention of the more recent MRI and SPECT evidence. Similarly, the more recent work undertaken by clinical psychologists carrying out detailed psychometric assessments of these patients has provided good supportive evidence for the reality of the continuing cognitive and performance problems that such patients have, often for prolonged periods after an apparently mild injury. The authors present a wealth of clinical and psychological data in a clear and lucid manner and the layout progresses naturally to

the helpful chapters on assessment and management. The prose style is good, the points the authors wish to make are clearly presented, and the book as a whole is helpful and inclusive. It might usefully have been more lavishly illustrated—for example, by some of the more impressive pathological material. I consider it to have earned a place on my bookshelf and I can recommend it for all those of us who have an interest in this condition and its often unfortunate consequences.

DAVID HARDY

**McAlpine's Multiple Sclerosis. Third Edition.** By ALASTAIR COMPSTON *et al.* (Pp 592, £105.00). Published By Churchill Livingstone, London, 1999. ISBN 0-443-05008-2.

For those not versed in the history of this text, Douglas McAlpine, Nigel Compston, and Charles Lumsden, in 1955, authored its forerunner *Multiple Sclerosis*. This was then succeeded by two editions of *Multiple Sclerosis: a Reappraisal* with the addition of E D Acheson to the authorship. The first edition of its offspring *McAlpine's Multiple Sclerosis* appeared in 1985. This current edition is inextricably linked to its past; its principal author, Alastair Compston, being the son of Nigel to whom the book is dedicated. Bryan Matthews, a current contributor, was the main author of the first edition.

Enough of the history, what of the book? As internationally recognised experts in their specific areas of multiple sclerosis, the present group of authors requires no introduction. The book contents have changed considerably since I first acquired the 1965 edition that concentrated on epidemiology (including a fold away map), clinical studies, and chemical pathology. The present text, lavishly illustrated, contains a balance of genetics, neurobiology, and pathophysiology as well as maintaining, for the generalist, authoritative sections on epidemiology, clinical presentation, diagnostic methods, treatment, and management.

Alastair Compston's initial chapter, itself a literary gem, elegantly sets the scene, outlining the early clinical and pathological descriptions of disease as well as the experiences of sufferers from the worlds of medicine and the arts. He goes on, in subsequent chapters, to discuss epidemiology, pathogenesis, and treatment. In relation to treatment he comprehensively reviews the evidence for disease

modifying therapies and, with the aid of a particularly memorable figure (14.8), addresses the symptomatic treatments available for both early and late disease. Bryan Matthews reviews the symptoms and signs of multiple sclerosis and its differential diagnosis. As would be expected, from his vast experience and clarity of writing, these sections are of great practical value—for example, the description of the warning signs (red flags) that should lead to diagnostic caution. Ian McDonald addresses imaging and other diagnostic techniques as well as pathophysiology of disease. These chapters reflect his own career at the forefront of electrophysiological investigations and thereafter the recognition and development of the potential of MRI, both diagnostically and in the understanding of disease mechanisms. George Ebers writes on the natural history, drawing on the literature and his own seminal work with Brian Weinshenker. Finally, and perhaps for the clinician most imposingly, Hans Lassman and Hartmut Wekerle describe the immunology and current state of experimental models with great clarity.

I am reminded, when praising a book so fully, of the dangers of sycophancy. Indeed, as Groucho Marx once wrote to an author pleased with his review "I am delighted that you are delighted that I am delighted". Of course there are omissions, the authors accept that while trying to be comprehensive they have delved into their specific areas of interest. With increasing specialisation in multiple sclerosis care within the United Kingdom, there is disappointingly nothing on how to develop a service and only a page on rehabilitation and the role of therapists (although evidence based medicine possibly justifies no more). There is also no mention of the economic burden of disease or the cost benefit and cost utility of available treatments and multiple sclerosis services.

These are, however, minor criticisms and the authors must be warmly congratulated on producing an outstanding reference text that Nigel Compston and his original coauthors would be immensely proud of, their intention at the outset being that of simulating interest "in the ever widening field of demyelinating disease". This book clearly fulfils that legacy and definitively presents the current state of knowledge. In their preface, the authors state that the final solution to the problems of multiple sclerosis, in particular more effective treatments, must await another edition (or more). Indeed, Dan Quayle might well have

been referring to multiple sclerosis when he famously once said, "there are a lot of uncharted waters still out there in space".

IAN BONE

**Advances and Technical Standards in Neurosurgery. Vol 25.** Editor in Chief F COHADON. (Pp 241). Published by Springer-Verlag, Wien, 1999. ISBN 3-211-83217-3.

Advances and Technical Standards in Neurosurgery was created in 1974 as an adjunct to the European postgraduate training system for young neurosurgeons. It has also proved popular with accredited neurosurgeons wishing to keep up to date with recent developments in the field. The first half of each volume reviews topics in which important advances have been made, and this is followed by in depth reviews of topical subjects from experienced clinicians.

The advances section begins with a review from Lausanne of the delivery of neuroactive substances to the CNS using the technique of encapsulation of xenogenic cells to avoid the problems of immune rejection. Possible applications in pain relief and amyotrophic lateral sclerosis are discussed. Fries and Perneczky then present the Mainz experience with rigid endoscopes, both for conventional procedures such as third ventriculostomy, cyst drainage, and tumour biopsy, and then discuss newer applications such as endoscope assisted microneurosurgery of aneurysms, tumours, and as an aid to microvascular decompression of cranial nerves in the posterior fossa. The final chapter in the first section presents the history and technique of chronic deep brain stimulation for movement disorders, reviews the results from Grenoble, Lille, and Creteil, and compares the outcomes with ablative surgery and neural transplantation. In the technical standards section there are reviews of recent advances in the treatment of CNS germ cell tumours, the surgery of hypothalamic gliomas, and approaches to the anterior cranial fossa with preservation of olfaction.

The quality of reviews in this book is excellent. Each is by a renowned expert in the field, and is well referenced for further reading. Those not already familiar with this series will find it both informative and thought provoking.

ROBERT MACFARLANE